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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/862,571	05/21/2001	Glenn McGall	AFMX-P02-038	9482

42145 7590 11/29/2006

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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/862,571	MCGALL ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Appeal Brief of 08/31/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,43 and 44* is/are pending in the application.

4a) Of the above claim(s) *4,5,8,10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,7,9,12,43,44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/27/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the Appeal Brief filed on 08/31/2006, PROSECUTION IS HEREBY REOPENED. The following rejections are applied as set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

Status of Claims

2. Claims 1-12,43,44 are pending.

During the prosecution of the application, applicant elected, without traverse, Group I, claim 3, together with linking claims 1,2,6-9,12. Claims 4,5,8,10,11 remain withdrawn from consideration. Further, in regard to election of species, applicant elected photolabile protecting groups, and compound of Formula II. Claims reading on the elected species are 1-3,6,7,9,12. Claims 1-3,6,7,9,12,43,44 are addressed to the extent they read on the elected species.

Claim Rejections - 35 USC § 112, first paragraph.

3. Claims 1-3,6,7,9,12 are rejected under 35 U.S.C. 112, first paragraph, as based on specification which is not enabling. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims, as drawn to elected species (see claim 9), are drawn to reducing non-specific binding to an oligonucleotide chip by replacing an oligonucleotide protective group with a negatively charged phosphate group by removing protective group and reacting thus formed active site with a phosphoramidite of formula II.

The specification does not provide support for the claimed effect of reducing non-specific binding by introducing negatively charged phosphate groups. The only example present in specification demonstrates reduction of binding of a specific protein, namely fluorescent protein conjugate phycoeretrin-streptavidin (Example 1[1]). The non-specific background binding does not significantly change with introduction of a phosphate group (compare second and forth rows of Table I, where "m" changes from 0 to 1). The claimed method is supposed to work on arrays testing biological samples. A biological sample is blood, urine, tissue, etc. As any of the molecules present in such sample is capable of binding to the surface of the array, the question is whether specification describes or provides guidance for the claimed universal effect of the

[1] Note that Example 1 does not illustrate the elected embodiment of the method.

negatively charged phosphate residues against non-specific binding of any of plethora of molecules capable of non-specific binding.. Evidently, biological samples contain plethora of molecules differing both in their chemical activity (i.e., with different affinity to react with phosphate group), and charge (i.e., negatively or positively charged). Thus, any positively charged molecule, e.g. a positively charged protein, would be attracted, rather than repulsed by the negative charge of the phosphate group, the effect that would increase rather than decrease non-specific binding. Specification does not provide any guidance on how to achieve reduction of binding by replacing an oligonucleotide protective group with a negatively charged phosphate group.

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

Response to arguments

In the course of prosecution, applicant pointed out that Table II is supporting the method as claimed, and asserted that "the specular background was almost completely eliminated when a number of negatively charged phosphate residues was included throughout oligonucleotide array" (p. 11, last full paragraph of the response). Examiner disagrees. Table 2 illustrates effect of increase in parameter "n", which, unlike parameter "m", does not include phosphate groups (see specification, p. 42, bottom). Further, applicant alleged that Table 2 demonstrates decreases binding of "insoluble

metal salts". Examiner failed to identify discussion of binding of "insoluble metal salts" in the discussed section of specification. Furthermore, applicant, surprisingly, declared that the feature shared by "insoluble metal salts" and "most proteins" is a "hydrophobic or negatively charged surface", and by due to such characteristic negatively charged phosphate group can be easily recognized as capable of reducing non-specific binding. Examiner questioned scientific reasoning behind both of these statements and invites applicant to provide references confirming their validity.

Further, in response filed 05/02/2005 applicant discussed results presented in Tables I and II and asserts that increase in the amount of negative charges improves signal to noise ratio. This argument was not deemed convincing as the point of the rejection is not that increase in the amount of negative charges always fails to reduce no-specific binding (and thus to improve signal to noise ratio). Rather, the point of the rejection is that the breadth of the claims encompasses interaction of the array with any sample, and as any biological sample (e.g., blood, urine, tissue, etc) contains plethora of molecules differing, at least in their charge (i.e., negatively or positively charged), it seems more likely that any positively charged molecule, e.g. a positively charged protein, would be attracted, rather than repulsed by the increase in the negative charge of the array, the effect that would increase rather than decrease non-specific binding. Applicant, in the response, does not address the issue of the variety of binding molecules of varying nature in the sample; rather, applicant discusses effect of varying surface charge of the array on its interaction with the same sample.

Further, in Appeal Brief, applicant asserts that because oligonucleotides naturally possess plurality of negative charges, it is unreasonable to expect that adding a single negative charge will have an appreciable effect on the array's affinity to positively charged molecules. Examiner disagrees. The instant claims are not directed to naturally occurring oligonucleotides; rather, the oligonucleotides assembled per the claimed method possess plurality of protective groups removal of which creates at least one negative charge. The latter, in Examiner's opinion, would attract, rather than repulse any positively charged molecule (e.g. a positively charged protein in a blood sample - the effect that would increase rather than decrease non-specific binding.

Applicant further argues that because "proper functioning of a biological system depends upon specificity of interactions between nucleic acids and other molecules, it is advantageous to make an oligonucleotide on the array more closely resemble a nucleic acid found *in vivo*". Examiner is not clear about the relevance of this consideration to the method of reducing non-specific binding to an array as claimed.

Claim Rejections - 35 USC § 102 and 103.

4. Claims 1,2,6,9,43,44 are rejected under 35 U.S.C. 102(b) as anticipated by Gamble et al (US 5981733).

The instant claims are drawn to method for reducing non-specific binding of a molecule to an oligonucleotide array by replacing one of protecting groups with a negatively charged phosphate residue.

Gamble et al (US 5981733) teaches method of synthesizing oligonucleotide array wherein protecting groups in a particular location are removed, phosphoramidate group is introduced into thus activated site and the phosphoramidate group is then oxidized into a phosphate group (i.e., the same chemical synthesis via phosphoramidate as in the instant method) .

Under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process. See MPEP 2112.02. In the instant case, the method of Gamble replaces protective groups with negatively charged phosphate residues same as the claimed method; as such the method of Gamble provides negatively charged phosphate residues which reduce non-specific binding.

5. Claims 1,3,7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamble et al (US 5981733) in view of US 5959098, or US 5,658,734, or 5,445,934, or US 5550215.

Regarding claims 3,7, Gamble does not specifically teach producing the initial plurality of oligonucleotides on a surface of the array by light sensitive methods comprising adding and removing photolabile protective groups. Such light sensitive methods, however, are well known in the art. See, for example US 5959098 (claims 1,6,7,10), or US 5,658,734 (claim 1) , or 5,445,934 (claim 9), or US 5550215 (as discussed below). A person of ordinary skill in the art, possessed with the understandings and knowledge of methods of preparing polynucleotide arrays reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to use photolithographic methods recited in the claims.

6. Claims 1-3,6,7,8,43,44 are rejected under 35 U.S.C. 102(e) as anticipated by US 5550215.

US 5550215 teaches method of preparing polymers on a substrate. Polymers can be, for example, oligonucleotides (claim 1). Oligonucleotides are prepared by, e.g, phosphoramidate method (see Definitions, paragraph #5) wherein a protective group PG is removed, phosphoramidate agent is added and phosphoramidate derivative is oxidized to phosphate by iodine (see col. 13, lines 5-9).

Regarding claim 2, solid support can be any material having a rigid or semi-rigid surface or surfaces (Definitions, #7)

Regarding claims 3,7, the process can be light directed using protective groups which are photolabile (claims 7,15)

In the instant case, the method of Gamble replaces protective groups with negatively charged phosphate residues same as the claimed method; as such the method of Gamble provides negatively charged phosphate residues which reduce non-specific binding.

As in the rejection over Gamble above, although the method of US 5550215 does not address directly reduction in non-specific binding, under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process. See MPEP 2112.02. In the instant case, the method of US 5550215 replaces protective groups with negatively charged phosphate residues same as the claimed method; as such the method of US 5550215 provides negatively charged phosphate residues which reduce non-specific binding.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Borin, Ph.D.

Primary Examiner

Art Unit 1631

mlb